PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference Case 21796	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/008609	International filing date *(day/month/year)* 30.07.2004	Priority date *(day/month/year)* 07.08.2003
International Patent Classification (IPC) or national classification and IPC C07K1/22, C07K1/32, C07K14/47, C07K14/74, G01N33/569, A61K38/00, A61K39/00		
Applicant F. HOFFMANN-LA ROCHE AG et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
31.01.2005	01.08.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Rutz, B Telephone No. +49 89 2399- 7828

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/008609

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-78 as originally filed

   Sequence listings part of the description, Pages

   1-104 as originally filed

   Claims, Numbers

   1-29 as originally filed

   Drawings, Sheets

   1/5-5/5 as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1,14-19,23-29 (all partially), 3-9,11,13,20-22 (all complete)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1,14-19,23-29 (all partially), 3-9,11,13,20-22 (all complete)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☒ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 2,10,12 (all complete), 1,14-19,23-29 (all partially) .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,14-16,19,24-28
	No:	Claims	1,10,12,17,18,23,29
Inventive step (IS)	Yes:	Claims	2,14,24-27
	No:	Claims	15,16,19,28
Industrial applicability (IA)	Yes:	Claims	1,2,10,12,14-19,23-29
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: DATABASE Geneseq [Online] 29 January 2004 (2004-01-29), "Human Protein P13284, SEQ ID NO 10787." XP002305086 retrieved from EBI accession no. GSN:ADD45354 Database accession no. ADD45354 & WO 03/016475 A

D2: DATABASE Geneseq [Online] 22 April 2004 (2004-04-22), "Human apoptosis-associated protein SEQ ID 154." XP002304913 retrieved from EBI accession no. GSN:ADI62711 Database accession no. ADI62711 & WO 03/058021 A

D3: CHICZ R M ET AL: "SPECIFICITY AND PROMISCUITY AMONG NATURALLY PROCESSED PEPTIDES BOUND TO HLA-DR ALLELES" JOURNAL OF EXPERIMENTAL MEDICINE, TOKYO, JP, vol. 178, no. 1, 1 July 1993 (1993-07-01), pages 27-47, XP002069888 ISSN: 0022-1007

D4: WO 93/18153 A1 (SMITH, GEOFFREY, LILLEY) 16 September 1993 (1993-09-16)

D5: DATABASE Geneseq [Online] 19 August 2002 (2002-08-19), "Human peptide encoded by genome-derived single exon probe SEQ ID 30218." XP002315338 retrieved from EBI accession no. GSN:ABG40553 Database accession no. ABG40553

D6: DI BARTOLO, V. ET AL: "Binding of human GM-CSF to synthetic peptides of the alpha subunit of its receptor" JOURNAL OF RECEPTOR AND SIGNAL TRANSDUCTION RESEARCH , 16(1 & 2), 77-92 CODEN: JRETET; ISSN: 1079-9893, 1996, XP009043176

1. Subject matter

Present application relates to the identification of rheumatoid arthritis related MHC class II associated peptides. Said peptides are identified following incubation of dendritic cells with synovial fluid from RA patients (non-erosive vs. erosive), immuno-affinity purification of MHC class II complexes, acid elution of peptides and mass spectrometry. *Inter alia* the application describes such peptides derived from interferon-gamma-inducible lysosomal thiol reductase (also called GILT or IP30; SEQ ID NO: 40), from the Interleukin-1 receptor and from the GM-CSF/IL-3/IL-5 receptor.

2. Novelty (Art. 33(2) PCT)

2.1. Prior art D6 describes a peptide which is identical to present SEQ ID NO: 71 and comprises SEQ ID NO: 111 (see Table 1).

Claims 1 and 12 lack novelty over D6 (Art. 54 EPC).

2.2. Prior art D4 and D5 both disclose short sequences which comprise SEQ ID Nos: 68 and 109. The designation "MHC class II antigenic peptide" appears not suited to exclude said short prior art sequences from the scope of present claims 1 and 10.

Claims 1 and 10 lack novelty over either one of D4 or D5 (Art. 54 EPC).

2.3. Claims 17, 18 and 29 lack novelty over D1 which describes a protein which is identical to present SEQ ID NO: 40 and which comprises SEQ ID NOs: 1-3 and 49 (D1, SEQ ID NO: 10787). Expression vectors and host cells are equally disclosed in D1.

2.4. Claim 23 lacks novelty over D1 which describes the medical use of proteins identical to present SEQ ID NO: 40.

3. Inventive step (Art. 33(3) PCT)

3.1. Claims 15-19 lack inventive step over either one of documents D4, D5 or D6 which describe sequences which comprise SEQ ID NOs: 68, 109, 71 or 111 of present application. The generation of antibodies directed to the disclosed peptides or the recombinant expression of said peptides is considered routine in the field.

3.2. Claims 23 and 28 lack inventive step over D2 because said document discloses the medical use of a protein which is 99.6% identical to present SEQ ID NO: 40 over a length of 250 (out of 261) amino acids. Furthermore, D2 states that detection of the polynucleotides and polypeptides of the invention can be used for diagnosis of inter alia rheumatoid arthritis. It was therefore obvious for the skilled person that the slightly variant protein of present application could be used as a marker for RA.

3.3. Claims 1, 2, 14-16, 19 and 24-26 as far as they concern subject matter related to MHC class II antigenic peptides with SEQ ID NOs: 1-3 or 49 are considered novel and inventive. The prior art mentions only two examples of MHC class II antigenic peptides derived from the GILT protein (D7, table 2). However, said peptides are bound by HLA-DR3 and not by HLA-DR1 as in present application. Furthermore, they are derived from a different region of the protein and no relation to rheumatoid arthritis is mentioned.

3.4. Claims 14, 23-25 and 27 as far as they concern subject matter related to MHC class II antigenic peptides with SEQ ID NOs: 68, 71, 72 or 109 are considered novel and inventive because the prior art contains no indication for the existence of MHC class II antigenic peptides of this sequence or their relation to rheumatoid arthritis.